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Thesis

THE PARASITIC FAUNA OF HAMSTERS OF THE GENUS CRICETUS

by

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Introduction

The hamster has been found to be a satisfactory laboratory animal because of its susceptibility to many human diseases such as leishmaniasis, tuberculosis, and Weil's disease; and because of its clean habits, prolific litters, and its endurance during infections.

The history of hamsters in the United States is short, these animals having been in this country only for the last 10 years. All the golden hamsters, Cricetus auratus Waterhouse 1839, now in captivity originated from one pregnant female captured in Allepo, Syria, in 1930(Morton 1943). These animals are nocturnal in nature, live in deep underground burrows and in fields, and feed mainly on grains which they store in their nests. They are a serious crop pest to farmers. Their distribution ranges from Europe through Asia Minor to China and the surrounding countries.

It is the purpose of this thesis to present a description of the parasites found to be either naturally or experimentally infective to hamsters. Since these animals are being used in greater numbers as experimental animals today, it is essential to know the parasitic fauna of hamsters ascompletely as possible, especially those which are parasitic also in man. Infection experiments to be described below add to our knowledge of hamster parasites.

Chapter I. LEISHMANIAE

1. Susceptibility

When the hypothesis of a rodent reservoir of an infection suggests itself, a study of the susceptibility of the animals involved in infection is desirable.

Smyly and Young (1924) were the first to report that the Chinese hamster, Cricetulus griseus, was very susceptible to kala-azar. By using large numbers of animals, they were able to show that the intraperitoneal route is the most certain method of infecting hamsters, an infection resulting in 91% of 89 cases. They noted that the parasites originally inoculated into the peritoneum were able to persist for about 30 days after they were introduced. Two hamsters were infected by the intrapleural route, one after 15 and the other after 67 days. The infections in each case were detected by liver puncture.

Hindle and Patton (1926) succeeded in demonstrating the infection of three Chinese hamsters by means of subcutaneous injection. They found that, in spite of the large number of parasites in the spleen and liver and the spleen being greatly enlarged, the animals seemed to remain in good health for long periods of time. No tendency to spontaneous recovery was observed. Infection via the percutaneous route was attempted, the results being negative. They also found that the hamsters were susceptible to the flagellate form if they were inoculated intraperitoneally.

The giant hamster, Cricetus triton, was found to be very

highly susceptible to infection with Leishmania donovani Laveran and Mesn. 1903 by Young and Hertig (1926). Moreover, these infections showed no tendency also to spontaneous recovery over a long period of time.

Mayer (1926) was able to show that the European hamster, Cricetus frumentarius Pallas 1811, is also suitable as an experimental animal because of its high susceptibility to kala-azar infection. Although Cricetus frumentarius is disputed to be different from Cricetulus griseus, Mayer believed it to be only a "large mouse substitute" for it.

Mayer (1929) attempted to prove whether hamsters were very susceptible to infection with Leishmania tropica Wright 1903, the causative agent of oriental sore. The inoculation of several hamsters resulted in the formation of multiple skin ulcers of the skin in the region of the belly. These ulcers contained many parasites. Further changes in the skin were not observed. In this way he established the susceptibilty of hamsters to this parasite. Results of tests whether a general infection also could be established by intraperitoneal inoculation were not very conclusive. The hamster, however, seems to be more suitable for research of kala-azar than it is for oriental sore.

In South American leishmaniasis, caused by Leishmania braziliensis Vianna 1911, single and multiple lesions are found characteristically on the exposed parts of the body, and no invasion of the viscera by the parasites has ever been re-

ported. Of the numerous experimental attempts to produce this disease in various animals, only a few have met with much success. The greatest fundamental problem has been to find an animal that is uniformly susceptible to cutaneous infection, thus enabling one to carry out studies on the transmission, immunology, and pathology of the disease.

In 1942, Fuller and Geiman, experimenting with the susceptibility of three strains of Leishmania braziliensis, found that Syrian hamsters were not infected by intraperitoneal inoculation of culture material. Out of 14 hamsters which were injected subcutaneously, only 3 developed skin lesions.

Kurotchkin (1931) proposed the hypothesis that, aside from individuals possessing natural immunity, the susceptibility of hamsters to kala-azar may be termed as absolute (100%). He found that in each group of inoculated hamsters, some of them do not become infected, thus indicating a trace of natural immunity in them.

No apparent protection against infection seems to be demonstrated when hamsters are first immunized by means of vaccines and then inoculated with viable parasites. On the contrary, Kurotchkin believes that the uniformly high percentage of infection among "immunized" animals indicates that hypersensitivity may play an important role in the susceptibility of kala-azar after preliminary immunization.

2. Epidemiology

The discovery by Young and Hertig (1929) that a common field rodent of the Chinese endemic area, the hamster, was extremely susceptible to infection with Leishmania donovani, whereas infection of other animals had been uncertain, pointed at once to the possibility of this animal and its allies being a reservoir of the disease. This situation would tend to explain the rural and sporadic incidence of the disease as found in China.

On this basis, Young and Hertig formulated the hypothesis that a field rodent, possibly the hamster, is a primary reservoir of leishmaniasis and that the disease is transmitted from rodent to rodent by means of one of its ectoparasites. Moreover, it was formulated that such a field rodent goes from field to grain-stacks, harvested stores, and buildings in villages where it may infect either house rodents or man directly by means of its ectoparasites.

The testing of this rodent reservoir-ectoparasite hypothesis involved the search for naturally infected hamsters collected in or around the villages infected with Leishmania. It also involved a study of the ectoparasites of such rodents with regard to their capabilities as vectors, and the determination of the susceptibility of house and field rodents to infection with leishmaniasis.

No evidence was obtained in support of the rodent reservoir

ectoparasite hypothesis. The hamster was shown not to be a reservoir of the disease, and no other rodent was found to play the the role. All attempts to transmit leishmaniasis from hamster to hamster by means of various ectoparasites, including fleas, failed completely.

Transmission problem-

a. Oral route

Previous successful experiments which have a bearing on the possibility of infection with Leishmania donovani via the intestinal tract have been done by Archibald (1914) on monkeys, Cornwall and Le Fienais (1916) on white rats, and Knowles, Napier and Das Gupta (1923).

Shortt, Craig, Smith, et al (1928) did experiments on the transmission of leishmaniasis via the oral route. Hamsters were given about two cc. of mixed liver and spleen emulsion by way of the mouth. One year later they were killed, apparently in good health. The spleen was enlarged four times its normal size. Spleen, liver, and bone marrow contained numerous Leishmania donovani and the parasites were easily demonstrated in smears made from the small intestine. The spleen and liver yielded rich cultures of Leishmania.

Prior to 1928, probably only four successful experimental transmissions of Leishmania donovani via the oral route were recorded in the literature: Archibald in 1914; Cornwall and Le Fienais in 1916; Knowles, Napier, and Das Gupta in 1923; and Shortt, Craighead, Smith, et al in 1928. Khaw (1930) checked

the conflicting results of previous workers. The results of his oral route experiments yielded 12 infected hamsters out of 14. In these experiments, evidence of infection became apparent on the seventh day after feeding the parasites to the hamsters. General parasitization was observed on the fifty-first day. The majority of the hamsters died within the period of one hundred to two hundred days, the course of the infection being the same as that after infection by the intraperitoneal route.

In 1931, Khaw produced infection of hamsters by feeding them with heavily infected carcasses. Ten hamsters were fed large portions of heavily infected carcasses of hamsters. Four died within a period of from 41 to 147 days after the first feeding. The remainder was killed approximately 153 days after the first feeding. Three of them had enlarged spleens and were heavily parasitized with Leishmania. A suggestion was put forward by Khaw that, even though this mode of transmission is negligible in man, it may be important in the maintenance of leishmaniasis in the hamsters.

The fact that Leishmania donovani in its flagellate stage has been proved capable of producing infection by the oral route suggested the advisability of investigating the possibilities of this method of transmission. So far as known, the flagellate form normally only occurs in nature in the insect host, Phlebotomus argentipes Agassiz 1846. This led Shortt, Smith, and Swaminath (1931) to determining whether

these insects, containing flagellate forms, are capable of producing infection by the oral route.

The insects were artificially infected partly by feeding on cultures of Leishmania donovani and partly with emulsions of spleen and liver of infected hamsters. One hamster was infected which showed no splenic enlargement, the infection being detected by cultures of the splenic material.

The success so easily obtained in experiments where the infective material was in the form of Leishman-Donovan bodies, contrasted with the negative results obtained in many experiments with the flagellate forms found in sandflies, has suggested that the ingestion of the Leishmania in the form of Leishman-Donovan bodies may be a specially adapted method to resist adverse conditions until the parasites have gained an entrance into the tissues of the host.

b. Conjunctival route

Mackie, Das Gupta, and Swaminath (1923) have produced transient infections in laboratory animals by the inoculation of infective material into the anterior chamber of the eye. However, so far as it is known, no previous case has been recorded of infection produced through the uninjured conjunctiva. Shortt, Craighead, Smith, et al. (1928) allowed a few drops of mixed liver and spleen emulsion of infected hamsters to fall on one eye of a hamster. One year later, the animal was killed in good condition. The spleen was found to be enlarged

four times its normal size. Examination of spleen smears revealed a moderate infection with Leishmania. Examination of the bone marrow showed a much heavier infection, and that of the liver a lighter infection. The hamster did not show any signs of local lesions of the eye.

c. Intratesticular route

In connectionnwith studies on Leishmania infections in experimental animals, Chu and Zia (1940) thought that the unexplored intratesticular route might be utilized to greater advantage than the intraperitoneal route usually employed in infecting hamsters experimentally. They found that the testes of full grown hamsters measure approximately six millimeters in length and three millimeters in width. It was also demonstrated that the testes could receive an injection of up to three-tenths of a cubic centimeter of an emulsion of infected liver or spleen. Out of twenty hamsters which were examined, nineteen showed the presence of Leishmania in the testes in from the fifth to the thirtieth day after inoculation; fourteen showed Leishmania in the bone-marrow from the seventh to the thirtieth day; and eight out of thirteen examined showed Leishmania in the liver and spleen. The results of this work indicate that the organisms multiply not only readily in the testes, but that the systemic involvement can be detected within two weeks after inoculation. This offers a new and convenient method of demonstrating the infection of Leishmania

in hamsters.

d. Arthropods as intermediate hosts

Of the numerous attempts made in the past to bring about the transmission of Leishmania donovani by the bite of Phlebotomus argentipes, all have failed, whether these experiments were on animals or on human volunteers. The reason for these failures is still not well understood.

However, it was reported in 1931 by Shortt, Smith, et al. that a successful transmission by the bite of this insect had been accomplished. The known life cycle of Leishmania donovani pointed to the probability that the bite of this insect was the method by which Leishmania donovani was conveyed to a new host. The experiment described below gave confirmation to this view.

Sandflies were infected by putting them on infected hamsters until they had finished their meals. Then the infected sandflies were fed on normal hamsters. The fact that only one out of forty-two hamsters became infected indicates that the infection rate by the bite of Phlebotomus argentipes is probably a low one. It was suggested by the authors that this would be one possible explanation for the slow spread of kala-azar in normal inter-epidemic periods and for its more rapid spread during an epidemic when the normal number of infective cases has increased to a maxim which results in a high percentage of infected sandflies. It was also suggested that the more rapid succession of passages of the parasites from man to

fly and vice versa during an epidemic would increase the virulence to a degree higher than that during non-epidemic periods. The authors believed that previous lack of success was due to the fact that kala-azar epidemics were terminating and thus the virulence of Leishmania donovani was in the process of decreasing.

The occurrence of natural infections of Phlebotomus chinensis with Leishmania flagellates had been reported previously by Chung and Feng (1939). In 1941, they reported further observations on naturally infected sandflies of the same species and the successful transmission to normal hamsters of visceral leishmaniasis which could not be produced in any previous experiments by subcutaneous inoculation with an emulsion of two such infected sandflies. Of the fifty sandflies dissected, thity-four or approximately sixty percent were found to be naturally infected with Leishmania flagellates. In all the sandflies the flagellates were found only in the midgut except in one in which case a heavy infection extended from the midgut to the proboscis. The flagellates recovered from two of these sandflies were inoculated subcutaneously into a normal hamster. After eight months, the hamster was killed. Smears made from the spleen, liver, and bone-marrow showed a large number of Leishmania donovani.

Young and Hertig (1926) attempted to transmit Leishmania by means of the lice, Haematopinus sp., but failed to obtain any evidence either of transmission or of development of the

parasites in the alimentary tract of the insect. These results combined with the rarity of this ectoparasites on hamsters indicated that in using the hamster for experiments in the transmission of Leishmania, lice may be neglected as an arthropod vector.

3. Histopathology of Leishmaniasis

Most of the histopathological studies as a result of leishmaniasis in hamsters has been involved with peripheral lesions, the peripheral blood, the role of the clasmatocyte which is a macrophage or large wandering phagocyte, oedema, and the metabolism of infected tissue.

Young and Hertig (1927) inoculated cultures of Leishmania donovani and Leishmania infantum Nicolle 1908, which originally produced visceral lesions only, intraperitoneally into Chinese striped hamsters (Cricetulus griseus). The resulting infections were visceral at first, with an enlarged spleen and liver and with Leishmania fairly abundant in the smears from the spleen, liver, bone-marrow, and heart blood. From about two months to a year later, bilaterally symmetrical lesions began to appear in the following order: (1) swelling of the feet including the digits; (2) swelling of the posterior half of the scrotum in males with subsequent ulceration, and in the female, infiltration and enlargement of the clitoris, especially with ulceration of the perineum; (3) swelling and later ulceration of the base of the tail; (4) similar swelling of the nose, but rarely with ulceration; and (5) swelling and ulceration of the margins of the ears. From the swollen tissues, Leishmaniae which were enclosed in large mononuclear cells were obtained in large numbers.

As the peripheral lesions developed, lesions of the vis-

cera tended to disappear, so that at the time of autopsy, the hamsters had livers and spleens which were normal in size and which were negative for Leishmania in smears. Inoculation of emulsions of these livers and spleens did not produce infection in hamsters.

Although Chinese hamsters are highly susceptible to infection with Leishmania donovani and develop typical lesions which seem to be comparable to those observed in human cases, the general health of the hamsters, however, is very slightly affected by the disease.

Therefore, Hu and Cash (1927-1928) thought it highly desirable to determine why the disease failed to produce in hamsters the same severe symptoms which Leishmania donovani produces in man.

Upon examination of a blood smear of a heavily infected hamster, they observed that no very marked anaemia or leucopenia was evident. The results of cell counts of fourteen normal and fifty infected hamsters showed that moderate anaemia and leucopenia occurs in infected hamsters. The most rapid reduction in erythrocytes takes place during the first month or so of the infection. The erythrocytes continue to be reduced in number until approximately the fifth month, after which time they show no significant change. The number of leucocytes declines gradually for the entire period.

After following the quantitative changes in the various

blood cells for seven months, it became evident that the hamsters were in some way protected from the severe anaemia and leucopenia which regularly developed in man. It is the opinion of Hu and Cash that the course of the infection in hamsters is fundamentally the same as that in human cases; but that the point at which the severe clinical symptoms appear is never reached in the hamsters.

The problem now was to determine why anaemia and leucopenia did not develop to a great extent. Hu and Cash (1927) and Cash (1928) found that the principal change in the peripheral blood was the appearance of a large number of cells called clasmatocytes, which contained many parasites. The clasmatocytes do not exist in large numbers in the peripheral blood of normal hamsters and are familiar to most scientists as the macrophages or large wandering phagocytes. The term clasmatocyte as used by Cash (1928) includes the fixed cells distributed throughout many organs, which have many of the same functions of the wandering cells. Examples of these fixed cells are the Kupfner cells of the liver and the phagocytic "endothelial cells" of the spleen, lymph glands, and bone marrow. Thus it was discovered that the clasmatocyte was a cell which was capable of phagocytizing the Leishmania, and which appeared in the peripheral blood only during an infection. They were also found to be present in large numbers in the skin and subcutaneous tissue of infected hamsters.

Continuing his work on the histopathology in experimentally infected hamsters with Leishmania donovani, Hu (1933) noted the marked parasitic infection and hyperplasia of the reticulo-endothelial system. He believed that undoubtedly this was the most important and characteristic feature of the histopathology of the disease.

Hu observed that the reaction was most striking in the organs in which the reticulo-endothelial tissue is normally most abundant, such as in the spleen, liver, lymph nodes, and bone marrow. The increase of plasma cells in the lymphoid organs plays an important role in the enlargement of the organs. The increase of the plasma cells is largely due to the presence of Leishman-Donovan bodies. In conjunction with the partial replacement of the bone marrow by reticulo-endothelial cells, Hu found that there was an increase of myeloid elements in the spleen. This increase is interpreted as being a compensatory hyperplasia for the loss of normal haematopoietic tissue in the bone marrow.

Hu also described a new type of reticulo-endothelial hyperplasia which consists of the formation of many elongated or spindle-shaped cells forming nodules or irregular cords and containing no or very few parasites. The cells in these two types of hyperplasia are morphologically different, even though they are genetically the same. The causes of this variation are not known. Moreover, these different types may

be found not only in different animals, but also in different parts of the same organ or in different organs of the same animal.

While working on the chemotherapy of experimental kala-azar, Goodwin (1945) observed that Syrian hamsters with long-standing infections of Leishmania donovani, sometimes developed severe symptoms of oedema. Ascites and distension of the mesenteries with fluid were the first symptoms of the condition. Later, gross oedema of the subcutaneous tissue developed and the skin was pulled down into a skirt around the flanks by the weight of the fluid it contained. The animal increased rapidly in weight through water retention and died in a short time. It was estimated that an adult hamster weighing eighty to one hundred grams might gain fifty grams in weight in the course of a week.

This condition appeared only after several months of infection with Leishmania, and not every animal was affected in this manner. The development of oedema did not depend upon the degree of infection as was demonstrated by parasite counts in splenic smears.

It was observed by Goodwin that oedematous animals exhibited proteinuria. The kidneys were pale and enlarged, and histological examination showed the degeneration of the glomeruli and the obstruction of the tubules with protein casts. It thus became evident that the severe loss of protein through the kidney is the chief cause of the oedema. It seems very

probable to Goodwin that the nephritis in this case is caused by the liberation of a toxin by the Leishmania under conditions of a chronic infection.

It had been shown by Adler and Ashbel (1934) that the flagellate stage of all the human Leishmaniae produced a considerable amount of glycolysis under both aerobic or anaerobic conditions.

In 1940 they undertook a study of the metabolism of livers and spleens of Syrian hamsters infceted with Leishmania donovani, Leishmania infantum, and of spleens of hamsters infected with Leishmania tropica. The metabolism of slices of the livers and spleens of hamsters infected with L. donovani and L. infantum, and of spleens infected with L. tropica, and also a suspension of Leishman-Donovan bodies was examined in a Barcroft-Warburg apparatus.

Infected tissue (liver and spleen) produced aerobic glycolysis which differed from that of normal tissue. The more intense the infection, the greater the glycolysis, both aerobic and anaerobic, particularly the former. It was also found that the oxygen consumption was increased. The individual infected cells produce the aerobic glycolysis, not the parasite. The Leishman-Donovan bodies freed from the tissue produced no appreciable aerobic glycolysis, in this manner differing fundamentally from the flagellate stage.

4. Treatment

The first compounds used for the treatment of infections with the various types of Leishmaniae were those of the tartar emetic group. These were later largely replaced by the pentavalent antimony compounds, since the antimony compounds were found to be less toxic. Moreover, they were also more in demand because of their greater efficacy and ease of administration. These compounds have been the prevalent ones for the past thirty years or so.

Recently diamidines have been employed with great success in the treatment of practically all types of leishmaniases. Adler and Tchernomoretz (1939) proved that 4:4'-diamidino stilbene has a definite chemotherapeutic action on Leishmania donovani in Syrian hamsters. In three animals which were sufficiently investigated, there was, as far as could reasonably determined, a complete disappearance of the infection from the spleen. This was the first instance of a drug not containing antimony with a marked chemotherapeutic action on an infection of Leishmania donovani. This therapeutic action is substantiated by the proven fact that infections of Leishmania donovani never regress spontaneously.

It was found that the therapeutic effect depends not only on the total amount of the drug injected, but also on the time-distribution of the total amount, which in this case was a two day interval. The optimum dosage and interval between

injections has not as yet been determined.

In treating an infection with 4:4'-diamidino stilbene, there did not seem to be any appreciable amount of destruction of the parasites in the first six days, even when large doses were used.

The most evident histological changes during the course of treatment of a hamster infected with Leishmania donovani was found in the spleen. Before treatment was started, the spleen was roughly enlarged to about four times its normal size. The Malpighian follicles were enlarged and their boundaries were irregular. The red pulp was congested and extremely cellular, containing in addition to numerous nuclei of reticular cells, lymphocytes, large monocytes, and varying numbers of plasma cells. One of the most striking features in the spleen at this stage was the relatively large numbers of megakaryocytes which were situated mainly near the periphery of the Malpighian follicles on the irregular border between the white and red pulp. In the spleen of the normal hamster, the number of megakaryocytes was very low.

After treatment had terminated and the infection was believed to be cleaned out, the above picture has not been altered to a great extent, except that the megakaryocytes have disappeared. The red pulp seems to be slightly less cellular, although it is still congested. Approximately eight to twenty days after the above stages, the spleen is still enlarged, its consistency firm, the follicles atrophied,and the most striking

change has occurred in the red pulp. The congestion has completely disappeared, the number of free cells has diminished, none or few of the plasma cells are found, and, compared to the first and second stages, the red pulp is strikingly less cellular, particularly around the sinuses, and contains greater proportions of connective tissue.

Harrison and Fuller (1946) found that the histological findings in the spleen of infected hamsters which are not treated were similar to those occurring in man. This suggested the fact that the changes which occur in the spleen as a result of treatment may be comparable in the case of both man and hamsters. In man, the enlarged spleen, as also in the case of hamsters, undergoes a marked reduction in size as the result of effective treatment. In man, there is only a small percentage of spontaneous recoveries, the mortality rate being very high; while, in the hamster, there are no signs of spontaneous regression of the disease.

Other diamidines which have been used with some success in human cases are 4:4'-diamidino diphenoxy propane (propamidine) and 4:4'-diamidino diphenoxy pentane (pentamidine).

Fulton (1944) found that 4:4'-diamidino stilbene, more commonly known as stilbamidine was very effective in what he described as "antimony-resistant" cases.

He experimented on hamsters infected with Leishmania donovani with a series of diamidine compounds. Stilbamidine, a recognized curative agent both in human and hamster infection,

was used as a control, since a satisfactory plan of treatment had been determined by experimentation in the case of hamsters.

He found that ten doses of twenty milligrams per kilo of stilbamidine resulted in a high percentage of cures. He found that 4:4'-diamidino-2-hydroxy stilbene was practically as effective as stilbamidine itself. The monoethyl and dimethyl derivatives of stilbamidine in suitable doses were also found to be curative, but not as effective as the parent compound. Little effect was demonstrated by the totane or diphenyl ureas.

The protection against infection with Leishmania will in this case be discussed under the heading of treatment. It concerns the cutaneous type of leishmaniasis. Vaccination against cutaneous leishmaniasis by inoculation of material directly from human lesions is a very old procedure, and, since the materials employed are uncontrolled, unpleasant results are occasionally produced from extensive secondary infections.

Katzenellenbogen (1942) therefore decided to inoculate Leishmania tropica into a number of uninfected residents in the district of the Dead Sea and uninfected recent arrivals, in an attempt to assess the value of the procedure in producing immunity.

The material used was either cultures of Leishmania tropica on Locke-serum-agar isolated from a local case, or of Leishman-Donovan bodies of the strain from the spleens of infected Syrian hamsters.

One hundred and sixty-seven persons were inoculated,

eighty-two with Leishman-Donovan bodies and eighty-five with cultures of Leishmania tropica.

These one hundred and fifty-two cases were followed up, and in one hundred and thirty-five of them a boil developed. The incubation period varied from less than two weeks to more than eight weeks.

Seven cases subsequently developed lesions remote from the site of the inoculation. However, it is very probable that in these cases the inoculation had been done during the incubation period of a natural infection with Leishmania tropica.

Out of thirteen tests to determine whether the subjects could be reinfected only one was successful. It was Katzenellenbogen's opinion that in hyperendemic regions newcomers and residents who have never been infected should be inoculated againstvthe cutaneous type of leishmaniasis.

A special note was made by Katzenellenbogen that the Leishman-Donovan bodies from the spleen of infected hamsters produced only local cutaneous lesions in human beings, without any signs of visceral involvement.

Chapter II. THE TRYPANOSOMES

1. Susceptibility

During the course of experiments on Leishmania in hamsters, Patton and Hindle (1926) observed in addition to the usual intestinal fauna, various other natural parasites. One of them was a trypanosome. In view of the fact that this parasite was found in the blood of the Chinese striped hamster, Cricetulus griseus, the name which they proposed for it was Trypanosoma cricetuli.

This parasite was found in more than one-third of the eight hundred hamsters observed. Occasionally, the trypanosomes were found in considerable numbers; ten or so in each microscopic field. No pathogenic symptoms were observed in the infected hamsters. The authors assumed that a balance had been established between the parasites and the host, as is the case in most natural infections.

In living preparations, the trypanosomes exhibit the characteristic wriggling motion of these parasites. In addition, it shows the rapid translatory avtivity of T. lewisi Kent 1900. However, the movements are more flexible than those of the rat trypanosome and the undulating membrane is more distinct.

In stained preparations, the trypanosomes appear to be monomorphic. The body is slender and prolonged into a pointed end posteriorly. The flagellum with the undulating membrane is free anteriorly for a comparatively short portion

of its length. The cytoplasm is almost free from granules. The kinetonucleus is large, elongated, oval in shape, and arranged transversely to the length of the body, approximately 10 microns from the posterior end. The blepharoplast is situated about the middle of the length of the body. The dimensions of the trypanosomes show very little variation, probably due to the fact that most of the specimens observed were in the non-reproductive stage. The average dimension for the total length of the trypanosome from the posterior end to the tip of the flagellum was 28 microns; for the width of the body at the blepharoplast, 2 microns; for the distance from the kinetoplast to the posterior end, 3.5 microns; for the distance from the kinetoplast to the center of the blepharoplast, 8.5 microns; and for the length of the free flagellum, 3-7 microns.

One of the trypanosomes for the hamster, Cricetus frumentarius Pallas 1811, was discovered by Wittich in 1881 and became recognized as a trypanosome by Robert Koch. Kempner and Rabinovitsch (1899) confirmed its similarity to the rat trypanosome, T. lewisi, and tried to transmit it to hamsters without success. Luhe, on the grounds of this unsuccessful attempt, addressed it as a separate species and named it Trypanosoma criceti.

In 1912 Noller examined T. criceti and did not find any morphological differences between it and T. lewisi. He found that not only the shape of the posterior extremities, but also

the size and shape of the trypanosomes and the shape and position of the blepharoplast agree perfectly. He tried to infect rats with T. criceti and did not succeed.

On the other hand, Engel (1923) compared both parasites in culture and found many important differences.

	Mean Total Length	Mean Length of Flagellum	Mean Width
T. lewisi	17.7 microns	12.8 microns	1.6 microns
T. criceti	26.8 microns	19.7 microns	1.1 microns

Zozaya (1929) also compared these two trypanosomes and many morphological differences were found. He found that T. criceti like T. lewisi in fresh preparations demonstrates a very swift motility, but moves by more extensive twisting coils or spirals and therefore appears ribbon-like from one end to the other. In fixed preparations, the differences were much more evident. The nucleus is more compact and lies in the middle and not at the boundary of the first and second thirds as in T. lewisi. Moreover, the various measurements agree very closely with those established by Engel.

The only other trypanosome which has been found in hamsters was that described by Nattan-Larrier and Noyer (1932). This trypanosome was found in 80% of the hamsters (Cricetus frumentarius) which they examined. The infections were revealed by means of cultures. The trypanosomes which were observed presented all the characteristics of Trypanosoma rabinowitschi Brumpt 1906. In examining the cultures, it was

found that these trypanosomes reproduce by multiple fission. The appearance of this phenomenon was seen in cultures of 20 days, 30 days, and 4 months. This method of multiplication was found to take place in the round, pear-shaped, and elongate forms, the process ending in the formation of 15-20 elements in rosettes. The authors believe that this trypanosome is comparable to the forms of Trypanosoma lewisi described by Delanoe in 1911, also.

2. Epidemiology

Most of the work done on the epidemiology of the trypanosomes of hamsters has been done with T. criceti.

Regendanz (1929) attempted to transmit T. criceti to hamsters by the oral route by means of the infected feces of the dog flea, Ctenocephalus canis Curtis 1826. No positive results were obtained. Moreover, he found that the rats which served as hosts of these fleas did not acquire infections with this trypanosome.

In his attempts to infect hamsters by subcutaneous and intraperitoneal inoculations of blood bearing trypanosomes, success was obtained in two out of four hamsters. Trypanosomes appeared in the blood 8-12 days after inoculation. It was also observed that multiple division was occurring at this time. Most of these infections were found to become chronic as time went on.

The termination of the period of multiple division of

the trypanosomes in the blood of infected hamsters was thought by Regendanz to be limited, as in lewisi infections of rats, through the appearance of an "inhibition of reproduction product." The long duration of chronic infection with hardly any change in the trypanosome content of the blood makes the hypothesis of a trypanosomolytic or trypanosomicidal antibody improbable. The spleen which produces these inhibiting products in lewisi infections was not found to play the determinating role in hamster infections, since the production of a renewed division of the trypanosomes through the splenectomy of chronically infected hamsters was not successful.

In the course of infections in hamsters, just as in the case of rat trypanosomiasis, three distinct periods are distinguishable: (1) an incubation period of 9-12 days with infection through flea feces or blood containing trypanosomes; (2) a period of division which lasts at the most 24 hours; and (3) a period of chronic infection which lasts over 5 months, during which all the trypanosomes are monomorphic.

Luhe, who named T. criceti, thought that most probably the vector for this trypanosome was transmitted by the flea, Ceratophyllus fasciatus Bosc 1800 which he has found to be a frequent ectoparasite of hamsters.

Noller (1912) found many mites of the genus Laelaps Koch 1836 on hamsters which were heavily infected with trypanosomes. These mites, when transferred to hamsters which were not infected, did not produce any new infections. In examining

numerous smears of these blood-sucking mites, no trypanosomes were found.

A number of fleas, Typhlopsylla assimilis Meinert 1896, which had rudimentary eyes were also found on the hamsters. In examining smears of these fleas, however, numerous unchanged and further developing trypanosomes were observed. He also observed the hamster trypanosomes in Ceratophyllus fasciatus and in the dog flea, Ctenocephalus canis. No conclusive evidence of these fleas as vectors has been established, since transmission attempts have not been performed.

3. Histopathology of Trypanosomiasis

Hoeppli and Regendanz (1930) found that the nature of the pathological changes in 37 experimental animals such as apes, dogs, hamsters, etc., did not depend upon the species of the trypanosomes, but upon the duration of the infection and to some extent upon the species of the experimental animal.

The most notable histological changes were myocarditis and pericarditis, with infiltration of numerous trypanosomes into the foci of the inflammation, and degeneration of the lens, iridocyclitis and conjunctivitis, with infiltration of the trypanosomes into the subconjunctival tissue, the ciliary body and the iris.

In the spleen and lymph nodes, the lymphocytes were gradually replaced by plasma cells, with subsequent infiltration of many macrophages. The cells which were found predomi-

nantly in the inflammatory changes of the organs were small round ones and macrophages accompanied by a few plasma cells and polymorphonuclear leucocytes.

Cellular infiltration was also found in the periportal tissue of the liver, in the meninges, in the choroid plexus of the lateral ventricle, in the interstitial tissues of the testes and the kidneys, in the striped musculature, and in the corium. Trypanosomes were also found in the blood vessels of almost all the organs in sectioned preparations.

4. Treatment

To date, very little work has been done on the chemotherapeutic effect of preparations against the trypanosome infections of hamsters. The only information which was found was the work done by Zozaya in 1929. He attempted to test the value of various chemotherapeutic preparations on a number of hamsters with natural infections. He found that Bayer 205, Neosalversan, and Antimony showed no or very little effect on infections of hamsters. The only preparation which had any noticeable effect was arsenophenylglyzin, as is the case for T. lewisi.

Chapter III. OTHER PROTOZOAN PARASITES OF HAMSTERS

Besides the Leishmania and Trypanosoma, many members of the class Sporozoa are parasites of hamsters. All but one of these parasites belong to the subclass Telosporidia. The one exception belongs to the subclass Neosporidia.

Many species of the order Hemogregarinida are parasitic in hamsters. In 1926, Patton and Hindle observed parasites which belonged to the genus Grahamella in the erythrocytes of hamsters, Cricetulus griseus. These parasites were relatively scarce, usually one erythrocyte being infected in every 40 fields of the microscope. In stained preparations, the parasites were rounded or comma-shaped. The erythrocytes which were found to be infected contained many of these parasites. When stained with Romanowsky stains, the parasites stained very intensely and in most of them one or more chromatin granules were seen. However, many of the organisms stained uniformly blue and gave no evidence of the presence of any chromatin material. This parasite was identified as being of the genus Grahamella because many bipolar forms, suggesting transverse division, were seen. It was distinguished from the genus Theileria by the absence of the quadruple forms of division characteristic of that genus. In view of the fact that this was found in Cricetulus griseus, the authors proposed the name Grahamella cricetuli for the parasite.

Noller (1912) found a large number of blood-sucking mites on hamsters, Cricetus frumentarius, which he had captured. He prepared a number of smears of these mites, in one of which he found many sporocysts of an haemogregarine. These mites, having fed only upon the blood of the captured hamsters, should have been receiving the parasites from these hamsters. He proceeded to examine fresh blood samples from the hamsters, but was unable to find of the parasites. A few months later, Noller noticed that there was an inflammatory swelling on one the ears. In examining the ear, he found that there was a white mass under a tightly stretched membrane and that the blood vessels of the ear were greatly enlarged. When the membrane was burst, a white purulent mass was obtained. Upon microscopic examination, this was shown to be composed mostly of polymorphonuclear leucocytes. Many haemogregarines were found in the leucocytes in stained smears. The ear healed within a week and the parasites disappeared from the ear. They were not found in the blood upon subsequent examination. Noller was also not successful in following further phases of sporogony in the hamster mites.

He was able, however, to study the morphology of this parasite from the smears which he had fortunately obtained. The free haemogregarines or merozoites were vermicular in shape, having an average length of 15-18 microns and a width of from 2-3 microns. In most of the cases, both ends were

bent toward each other so that they were crescentic in shape. The protoplasm was finely alveolar (feinwabig) and contained many metachromatic granules. The position of the nucleus was found to be nearly in the center.

The sporocysts from the hamster mites were oval and covered by a double membrane. The average length was 25-30 microns and the width was from 12-14 microns. The sporozoites lie within the sheath in varying numbers, from 12 to 25 in each sporocyst. The free mature sporozoites are much wider than the vermicular merozoites, their length being from 15-17 microns and their width from 2.5-5.0 microns. The protoplasm shows a clears alveolar texture. Moreover, the nucleus is usually larger, and in the anterior half of the sporozoite a thicker cytoplasmic region is observed. Noller decided that this was a new species and named it Leucocytogregarina criceti.

Zasukhin (1931) found three out of twenty-five hamsters, Cricetus cricetus Desmarest 1804, infected with Grahamia which were morphologically undistinguishable from G. alactagae. Sussuchin (1931) found Grahamia in hamsters of the species, Cricetus frumentarius.

Noller (1920) was the first to find Coccidia in hamsters. They were found in the hamsters, Cricetus cricetus. The size of the oocysts was from 18.02-22.0 microns by 11.0 microns. Noller considered them to be a species of mouse Eimeria, Eimeria falciformis, and named them E. falciformis var. criceti.

Yakimoff and Gousseff (1935) examined four hamsters, C.

cricetus, and found one of the animals to be infected. Upon microscopic examination, three types of coccidia were found.

In type 1, the form of the oocysts was round, the oocyst being covered by a smooth double membrane. The average size was 19.85 microns in diameter. However the majority of them were 24.4 microns in diameter. Two oval spores were present in each oocyst, their size being 14.4 by 8.1-9.0 microns, each containing 4 sporozoites. The oocysts of type 2 were less numerous than those of type 1. The size of these oocysts were 19.52-26.84 microns in length and 17.08-24.40 microns in width. Two round sporoblasts were found in each oocyst, their size being 12.6 microns in length by 10.9 microns in width. The oocysts of type 3 were very rarely found. The shape of this type was pear-shaped. The size was 24.40 microns by 19.52-20.74 microns. Unfortunately, they were not able to find any evidence of sporulation in this type.

They considered types 1 and 2 as belonging to the same species. The name which they proposed for this parasite was Isospora freundi, in honor of Dr. Freund of Prague. Since they were unable to find any signs of sporulation, they were not able to say which species type 3 belonged to or whether this type represented I. freundi.

The only neosporidian of hamsters belongs to the order Sarcosporidia. Patton and Hindle (1926) found these parasites in 8 out of approximately 300 hamsters, Cricetulus griseus. Their cysts were restricted to the subcutaneous muscles of

the back and pharynx, and relatively few in number, not more than 20 being found in any one animal. If the hair were removed, the cysts could be seen through the skin of the hamsters. The average size of the cysts was 1.5 by 0.2 millimeters. They were usually elongated and oval in shape. When the animal was killed and skinned, the cysts adhered to the inner surface forming conspicuous white spots. The cysts all contained large numbers of spores at a similar stage of development. Each spore was elongate and slightly curved, one end being rounded and the other end being pointed. In stained preparations, the nucleus was round and found lying near the roundedcend. In some cases, a vacuole or a clump of granules was found at the pointed end, and the cytoplasm was often filled with minute granules. The size of the spores was usually from 8 to 10 microns in length and 2 microns in width.

In an attempt to transmit these parasites from one hamster to another, a suspension of spores in saline was fed to 12 hamsters. Three died within 14 days and were negative. Another one died at the end of the 7th week. Upon examination, a few small cysts which contained spores were recovered from the subcutaneous muscles of the back. The remaining hamsters were killed four months after the experiment and all were negative. These results suggested, therefore, that the parasites were not transmitted by swallowing the spores, as in Sarcocystis muris Blanchard 1885, since the single animal which was positive had probably acquired the infection prior

to the experiment. Because of the fact that this parasite differed from other species, both in its host and in the site chosen for the development of the cysts, the authors considered it a new species and named it Sarcocystis cricetuli.

Sprinholz-Schmidt (1937) found a blood parasite in the hamster, Cricetus furunculus Pallas 1811. This parasite belongs in the group of uncertain protozoans, in that its proper position in the classification is not known. The only fact which is agreed upon is that it belongs in the class Sporozoa. Sprinholz-Schmidt made blood smears of these hamsters and upon examining them found endo-erythrocytic parasites of round, oval, pear-shaped, and Maltese-cross forms. In comparing the characteristic forms of this parasite with other species of Nuttallia described by various authors, he concluded that he had found a new species and named it Nuttallia cricetuli.

The round forms which he found constituted 41.8% of the total number of parasites. They represented inclusions which were usually found at the periphery of the erythrocyte. The protoplasm stained sky-blue and the chromatin mass stained a very dark red. The average size of these forms was 1.22 to 1.60 microns.

The oval forms made up 22.2% of the total number. They were a little longer in length and possessed one chromatin mass. The size of these oval forms was 1.25-2.0 by 0.8-1.0 microns.

The pear-shaped forms made up 34.3% of the total number.

Their contours were very regular and each had one chromatin mass. There were no double pear-shaped forms present. The size of these forms was from 2.22-2.44 microns by 1.1-1.5 microns.

The Maltese-cross forms were not often seen, their incidence being only 2% of the total number. They consisted of 4 pear-shaped fragments. The size of these forms was 1.88 microns.

The incidence of erythrocytic infection was found to be 1.5%.

Chapter IV. HELMINTHS INFECTIVE TO HAMSTERS

Cestodes are the most frequently found helminths in hamsters. However, a few members of the Trematoda and Nematoda were also found to be infective to hamsters.

The cestode first found in hamsters was Hymenolepis straminea Goeze (1782). This tapeworm is an ill-defined species since Goeze gave little information in his description. He stated that the parasite measured up to 8 inches in length, appeared as a narrow and delicate strobila, bore 4 suckers and a set of fine hooks on the scolex, and that the eggs contained distinct embryos. Dujardin (1845) summarized and elaborated upon Goeze's description. He found that the length of the strobila was 30 to 200 millimeters with a width of from 1.2 to 2.25 millimeters. The scolex bore 19 to 23 hooks which are 0.014 millimeters in length. The width of the scolex was 0.2 millimeters. The hosts of this cestode are usually Cricetus cricetus, C. frumentarius, and C. vulgaris which has been cited as being synonomous with C. cricetus.

The second cestode to be discovered in hamsters was Hymenolepis criceti Janicki 1904. Janicki gave a brief description of this species in 1904, but a fuller description was presented in 1906. This species of cestode was obtained from Cricetus cricetus. The length of this parasite was not given since the specimen was in fragments. The maximum width was found to be 0.44 millimeters. The scolex was large, with

a diameter of 0.314 millimeters. The rostellum was well developed with a row of 24 hooks upon it which measured 0.016 millimeter in length. The ratio of the length to the width of the mature segments was found to be 1:1.5, the last segments becoming square. The boundaries of the segments showed no distinct indentation. The excretory canals showed no transverse anastomosing. The genital pores were situated near the anterior margin of the segments. The thick ovary consisted of 2 massive lobes. The large seminal receptacle of the vagina was found to be regularly filled with eggs. The testes were large and easily seen. The ripe eggs which fill the entire proglottid were surrounded by 2 membranes, the diameter of the outer shell being 0.043 millimeter and that of the onchosphere being 0.025 millimeter. Janicki stated that there was no doubt that this new species was different from H.straminea, since it had relatively long segments, lacked projecting posterior borders of the segments, and had a narrower strobila.

Oldham (1929) described a new species, Hymenolepis sinensis, which he obtained from Cricetulus griseus captured in China. Oldham described this cestode as being up to 100 millimeters in length and semi-transparent throughout. The scolex was small, more or less rectangular in cross section, and from 0.08 to 0.12 millimeter in diameter. There were four suckers on the scolex with an outside diameter of00.043 to o.051 millimeter, more or less rounded and touching each

other. The rostellum was well developed, measured 0.046 to 0.048 mm. in diameter, and was armed with a single row of 20 hooks which measured from 0.022 to 0.024 mm. in length. The long and slender neck became segmented at a point 2 mm. from the scolex. The genital organs were first visible in the 40th to the 45th segment. Proglottids with fully developed male and female organs appeared at about the 300th segment. The genital pore was slightly posterior to the midpoint of the lateral border of the segment. The testes measured from 0.05 to 0.08 by 0.03 to 0.06 mm. and were arranged in the following manner: one posterior and poral, one posterior and antiporal, and the 3rd anterior and median to the posterior antiporal testis. The cirrus sac measured 0.1 mm. in length and passed dorsally to the dorsal and ventral vessels and longitudinal nerve. The ovary was compact and not markedly lobed and measured 0.13 to 0.14 mm. from one side to the other. The gravid segments were from 150 to 250 in number and measured from 0.54 to 0.88 mm. on the average. The total number of recognizable segments was 2,000 or more. The eggs were nearly spherical with an average measurement as follows: The outer membrane, 0.061 by 0.054 mm.;nthe inner shell, 0.036 by 0.027 mm.; the knob at the poles, 0.002 to 0.004 mm.; the onchosphere, 0.030 by 0.024 mm.; and the embryonic hooks, 0.014 to 0.016 mm. long.

In comparing the morphological differences between H. criceti and H. sinensis, Oldham thought that there was no doubt

that the cestode which he observed was a new species. He realized that the differences between H. sinensis and H. straminea were not as well marked, but that this was due to the fact that accurate information about the latter was lacking. He stated that, if one considered the geographical distribution of these parasites, added justification and support is given to considering this species a new one. H. sinensis occurs in China, Mongolia, etc., while H. criceti and straminea are parasites found in Europe and Asia Minor.

Another species of the same genus, Hymenolepis nana (Siebold 1852) Blanchard 1891, the dwarf tapeworm which is also parasitic in man, was found in the Syrian hamster, Cricetus auratus, by Stunkard in 1945. He examined a shipment of hamsters and found that eggs of H. nana were present in the feces of several animals. This species of tapeworm is directly infective to man and does not require an intermediate host as most of the tapeworms do. Therefore, Stunkard stressed the necessity for careful handling of these experimental animals. The infection, once acquired, may become very serious by means of auto-infection, a characteristic in the life cycle of this tapeworm.

Watson (1946) examined 160 hamsters which had been used for experimental infection with Leishmania. Nineteen of the 160 hamsters were found to be infected with H. nana, some of these hamsters being highly parasitized. One of the hamsters harbored 22 adult tapeworms. Watson believed that an incidence

greater than 11.9% would be found in other cases, since most of these hamsters belonged to one batch.

Yeng (1931) presented a report on the lesions produced by representatives of different groups of parasitic worms. The purpose of this work was to observe the manner in which the parasites attack the host and to observe the defense reaction of the host's tissue, if any. A portion of his work was done on the lesions produced by Hymenolepis nana on the hamster, Cricetulus griseus.

This parasite, found in the small intestine, possesses a rostellum bearing 21 to 22 hooks which do not disappear in the adult worm, as in some species of tapeworms. The scolex penetrates to the deeper layers of the mucous membrane, but does not reach the submucosa usually. In the process of doing this, the worm breaks off parts of the epithelium with its suckers and hooks at the place of fixation. This mechanical destruction only produces insignificant lesions. There does not seem to be any defense reaction set up by the host since no cellular infiltration around the scolex is observed.

Severinghaus (1928) experimentally infected hamsters with a trematode, using the blood fluke, Schistosoma japonicum Katsurada 1904. The intermediate host for this fluke is a snail, Oncomelania sp. Cercariae from infected snails were used to infect the hamsters experimentally. Infected snails were placed in large Syracuse dishes and allowed to stand.

Six hamsters were then placed in these dishes and allowed to splash around in the infected water for approximately half an hour, during which time the fork-tailed cercariae penetrated the skin. The hamsters were then removed and placed in separate cages. It had been previously determined that the viable cercariae from one snail would infect 6 hamsters. This density of infection produced on the average from 15 to 40 adult flukes in the portal system of the hamsters, a number not found fatal to these animals. All the animals were observed twice daily. Those which showed signs of serious symptoms were sacrificed before natural death occurred. Upon autopsy, all hamsters were found to be positive.

In 1932, Shulz found another trematode in the small intestine of Cricetus sp. Tobolsk. This was identified as Plagiorchis obensis.

Nematoda which have been found in hamsters either naturally or experimentally are Litomosoides carinii, a filariid parasite; Syphacia obvelata, an oxyurid parasite; and Heligmosoides travassos and yorkei, 2 trichostrongylid parasites.

Litomosoides carinii is a natural filariid parasite of the cotton rat, and is used extensively in investigating the chemotherapy of filarial infections. Williams and Brown (1945) showed that this parasite was transmitted from one animal to another by means of the tropical rat mite, Liponyssus bacoti. These workers supplied Hawking and Burroughs (1946) with a colony of infected rats. They were able to infect rats, find-

ing microfilariae in the blood 63 days after the first exposure to to infected mites. Some of these experimentally infected rats had as many as 50,000 microfilariae per cc. of blood. Hawking and Burroughs attempted to infect 3 hamsters, Cricetus auratus, by exposing them to infected mites for periods of 22-44 days. One hamster died within 39 days. Five worms measuring from 1.0 to 3.2 cms. in length, of both sexes, were found in the pleural cavities. Another hamster, killed on the 44th day, had 3 worms, 1 to 3 cms. in length, in the pleural cavities. In the case of the 3rd hamster, microfilariae were found when the blood was examined on the 70th day and on subsequent occasions. The number however was very small.

The development of L. carinii in the mite has been studied by Williams and Brown (1945). In the digestive tract of the mite, the microfilariae grow in length from 69 to 109 microns, not including the sheath. At the same time, there is a gradual increase in width from 5.5 to 7 microns. At this point in the development, there appears a sudden increase in width to 13.2 microns, thus forming a typical sausage form with a short sickle-shaped tail. The width continues to increase and individual variations ranging from 15.6 to 20.8 microns are found in those larvae which are 125 to 510 microns in length. From this point on in the development, the width seems to become fixed. Those forms which are presumed to be the infective stages usually reach a length of 800 microns. Other ectoparasites such as fleas, ticks, etc. were examined and

found not to harbor developing filariae.

Watson (1946) while examining 160 hamsters for helminths, found 83 animals were infected with the oxyurid nematode, Syphacia obvelata. Many of the hamsters were infected quite heavily. Since this species is also believed to be infective to man, Watson stressed that laboratory workers should handle experimental animals with caution, since the incidence of 51.9% for this oxyurid in hamsters is considered to be very high.

Schulz (1927), studying the helminth fauna of rodents of U. S. S. R., found that the hamster, Cricetus cricetus rufescens, was infected with a trichostrongylid parasite, Heligmosoides travassos which he described as new. He also found that the hamster, Cricetulus migratorius pulcher, were infected with the trichostrongylid, Heligmosoides yorkei, also described as new.

Chapter V. ECTOPARASITES OF HAMSTERS

Many natural ectoparasites of hamsters have been found. These ectoparasites consisted mainly of fleas, mites, ticks, lice, and in a few instances, of larval forms of the true flies.

Patton and Hindle (1926), in their work on leishmaniasis of hamsters, found numerous Haematopinus sp. Leach 1817 on only one individual. However, they believed that it probably exists on a small percentage of hamsters. In addition, they found a single specimen of Ceratophyllus, the species not being determined.

Regendanz (1929) was positive that the dog flea, Ctenocephalus canis, is also an ectoparasite of the hamster, because the hamster trypanosome develops in the alimentary tract of this arthropod. Noller (1912) stated in his studies on trypanosomes that he had found this flea on a few of the hamsters which he had examined.

Luhe (Zozaya,1929), who named Trypanosoma criceti, stated that the probable vector of this trypanosome was Ceratophyllus (Pulex) fasciatus Bosc, frequently found in the region of the cheek pouches. Noller (1912) also found Ceratophyllus fasciatus on many hamsters.

Wagnes and Ioff (1926) described a new species which they found on the hamster, Cricetulus furunculus Pallas 1811, and named it Ceratophyllus arvalis. Jordan (1929) described many new species. He found Ceratophyllus tesquorum spp. sungarius

on Cricetulus arenarius Desmarest 1804; Ophthalmopsylla jettmari, Rhadinopsylla dives, R. insolita, and R. tenella in the nests of Cricetulus spps.

Noller (1912) found many fleas with rudimentary eyes, identified as Typhlopsylla assimilis Taschenberg 1880, which had not been found on hamsters before. These fleas were found on the head of the hamsters, usually in the region of the mouth, cheeks, nose, chin, and the ears.

Jettmar and Lin Chia-Swee (1929) found fleas, Neopsylla bidentatiformis Wagner 1903, on hamsters of Cricetulus sp. They stated that these ectoparasites were able to transmit plague from hamster to hamster. Many unidentified fleas and mites were also found. The authors observed larval stages of these arthropods in the nests of the hamsters.

Noller (1912) found blood-sucking mites on hamsters which he had captured. They occurred on the throat, chest, abdominal surfaces, and preferably on the inner surfaces of the thighs. These ectoparasites were very easily seen with the naked eye, their length being from 0.4 to 0.7 millimeters. Many of them had relatively large and conspicuous ova in the abdominal region. Noller was not able to determine the species, but thought that they probably belonged to the genus Laelaps Koch 1836.

Ewing (1935) also found sucking lice on hamsters of China, Cricetulus andersoni. They were identified as Polyplax denticorius. He also stated that there is a possibility that

lice of the Eremophthurius sps. are ectoparasites of hamsters since these two genera are closely related.

Although many mites are ectoparasitic on hamsters, there are few instances of ticks being found on hamsters. Ixodes laguri was found on Mesocricetus brandti and Cricetus cricetus, by Kirschenblatt in 1936.

Kolpakova (1931) found larval stages of Rhipicephalus schulzei Koch 1884 on hamsters, Cricetus cricetus. These larval forms were found to be prevalent in May. The adults are found on man and other large mammals.

Rey (1933) recorded the presence of larvae breeding in the skin of a living hamster of Cricetus sp. In examination of the hamster, he discovered a hole in the skin which was 4 mm. in diameter and from which a passage led anteriorly. Eight cylindrical larval forms of flies were recovered from this passage. The larvae had a mean length of 1 cm. Further examination revealed that the skin passages led into the abdominal cavity and that in here more larvae were found. According to their appearance, these belonged to the genus Calliphora. He was unable to identify the species.

Chapter VI. RESEARCH ON THE EXPERIMENTAL INFECTION OF HAMSTERS

The Syrian hamster, Cricetus auratus, has been found to be a satisfactory laboratory animal for the study of many human diseases such as leishmaniasis, tuberculosis, Weil's disease, etc. Moreover, the hamster has been found to be very hardy, free from the usual laboratory infectious diseases, and capable of bearing young when only 67 days old.

The purpose of this experimental work was to add to the knowledge of hamster parasites. The parasites which were used in attempting to infect hamsters experimentally were those which had not been mentioned in the literature. They were Hymenolepis diminuta (Rudolphi 1819) Blanchard 1891, Trichostrongylus sp. Cobbald 1879, Trichocephalus trichiurus (Linnaeus 1771) Stiles 1901, Enterobius vermicularis (Linnaeus 1758) Leach 1853, Toxascaris leonina Linstow 1902, Trichocephalus vulpis (Froehlich 1789) Smith 1908, and Heterakis gallinae Dujardin 1845. The only ectoparasite used was Pediculus humanus capitis de Geer 1778.

Methods:

The eggs used in these infection experiments were obtained from wild rats, dogs, and man. The feces of the infected animal were collected, made into a suspension with water, and strained in order to remove the bulky waste material. A smear of this material was then examined. If egss were found to be present, they were identified and concentrated by either

the Faust zinc sulphate centrifugal flotation method or the De Rivas acid-ether centrifugal sedimentation method. The eggs were then removed to Petri dishes with tap water and allowed to embryonate. When the eggs were fully embryonated, they were fed orally to hamsters which had been previously examined in order to ascertain that they were free of parasites. Fecal examinations were made weekly to see whether any of the parasites had developed to sexual maturity in the hamsters.

In autopsying the hamsters, blood smears were first made, stained with Giemsa, and examined. The surface of the body was examined for ectoparasites. Finally all the internal organs were examined. If parasites were found, they were fixed in warm AFA fixative, stained, and then mounted. All the fecal material in the intestine was collected and examined to check whether any parasites had escaped notice.

Discussion and Results:

Hymenolepis diminuta

One hamster was fed eggs of H. diminuta directly on Dec. 11, 1948, in an attempt to omit the intermediate host which is believed to be possible in this family of cestodes. Fecal examinations were begun on Jan. 3, 1949. This hamster was found to have ova in the feces on Feb. 21, 1949. However, at no time after that were eggs found in the feces. Autopsy of this hamster on April 1, 1949, did not reveal the presence

of any tapeworms. There is a strong possibility that the tapeworm had developed and then passed out since the time necessary for this parasite to develop to maturity is 1 to 2 months, depending on the enviromental conditions. Two other hamsters were fed mealworms which are one of the intermediate hosts for this tapeworm in which the infective cysticercoid develops. Dissection of a few of the mealworms did not reveal the presence of any cysticercoids. Weekly fecal examinations and autopsy on April 1, 1949, did not reveal any tapeworms. From the fact that eggs were found in the feces of one hamster on Feb. 21, 1949, evidence is given that this cestode might develop directly from the eggs. In the case of the mealworms, there is the possibility that the cysticercoids did not develop.

Trichostrongylus sp.

The eggs of this species were found in wild rats. After the necessary 4 days to become infective, they were fed to one hamster on Dec. 11, 1948. Fecal examination at no time revealed eggs of this parasite. Autopsy on Apr. 13, 1949, also did not yield any trichostrongylids.

Trichocephalus trichiurus

Two hamsters were fed embryonated ova of T. trichiura which required 16 days to become infective. The material fed to the hamsters contained few eggs and this might explain why this parasite did not develop, as was borne out by fecal examinations and eventually autopsy on April 18, 1949.

Enterobius vermicularis

This particular infection experiment was most interesting because according to the literature the human pinworm has never been found to develop to the adult stage in rodents (Jones and Nolan, 1942). However, larval forms will develop and then pass out. The infective eggs were fed to 2 hamsters. on Feb. 4, 1949. One of the hamsters was found dead on Mar. 28, 1949, and apparently had been dead for 2 days. On autopsy, no parasites were found, the internal organs being badly decomposed. The other hamster was autopsied on Mar. 31, 1949. Twenty roundworms were found to be present in the cecum. They were fixed, stained and mounted. They measured from 8 to 11 mm. in length and 0.5 to 0.8 mm. in width. Within the cuticle could be seen the digestive tract with the characteristic esophageal bulb and the reproductive system consisting of coiled ovaries, the uteri and the vulva. There were cervical alae in the anterior part of the body. The posterior was drawn out into a fine point. Within the uteri, many eggs could be seen developing. One of the worms was mashed and examined. The characteristic pinworms could be seen which were oval and flattened on the ventral side. The eggs were not fully embryonated but partially developed. This is probably due to the fact that the necessary 2 months for the life cycle had not elapsed. If the animal had been autopsied 2 or 4 days later, the eggs would have most probably been fully embryonated.

Toxascaris leonina

On March 3, 1949, 2 hamsters were fed eggs of T. leonina, the ascarid of dogs, cats, and foxes, which required 8 days to become embryonated. One hamster was autopsied on April 18, 1949, and about 40 worms were recovered from the cecum. These were fixed and stained. Examination of these worms showed that they were larval forms. They varied from 5 to 8 mm. in length and from 0.3 to 0.4 mm. in width. No clear differentiation within these larvae could be seen because cell division seems to have been going on at a great rate. No eggs were seen developing in the reproductive system. The other hamster was autopsied on April 13, 1949, and no parasites were obtained. This was a surprise since the same infective material was used for both of these hamsters. One explanation is that the larval forms which might have been developing in this hamster passed out, indicating that this parasite does not develop into the adult form in hamsters. This phenomenon is characteristic of ascarids as illustrated by the fact that the ascarid of man, sheep, and the hog will develop in any of these three hosts as far as the larval stage, taking the migratory journey through the lungs, but will pass out immediately thereafter.

Trichocephalus vulpis

Eggs of this parasite which required 14 days to become embryonated were fed to 2 hamsters on March 15, 1949. Fecal

examinations and eventually autopsy on April 18, 1949, did not reveal the presence of trichocephalids. Since this was the second species of trichocephalids which was used for infection experiments, it is probable that this parasite is extremely specific as to hosts.

Heterakis gallinae

The last intestinal parasite used was H. gallinae, a nematode parasitic in chickens. Eggs which required 15 days to become fully embryonated were fed to 1 hamster on April 1, 1949. The hamster was autopsied on April 18, 1949, and was found not to be harboring any parasites. The life cycle requires 1 month to be completed. Therefore, larval forms at least should have been found if this parasite can develop in hamsters.

Pediculus humanus capitis

One hamster was exposed to 9 head lice, P. humanus capitis, on Jan. 15, 1949. One week later no lice were to be found, probably because the hamster had eaten them.

Conclusions:

It may be said that the hamster serves as an experimental host for at least the larval forms of Toxascaris leonina, and for the larvae and very possibly the adults of Enterobius vermicularis. No conclusive evidence was found that Hymenolepis diminuta develops in hamsters. However, the eggs found

during one of the fecal examinations and during none of the subsequent examinations, suggest that this tapeworm may develop in hamsters. Trichostrongylus sp., Trichocephalus trichiurus, Trichocephalus vulpis, and Heterakis gallinae did not develop in hamsters. All the hamsters were found to be free of ectoparasites which is probably due to their very clean habits. No parasites were found to be present in the blood. A suggestion is put forth that a full scale experiment be undertaken to prove conclusively that the human pinworm, Enterobius vermicularis, is able to develop in the hamster. Experiments might also be carried on concerning the ability of the malarial parasites to develop in hamsters. No reference was found in the literature about malaria in hamsters.

CONCLUSIONS

Hamsters are very susceptible to infection with Leishmania donovani in nature. They may be infected experimentally by the intraperitoneal, intrapleural, subcutaneous, oral, conjunctival or intratesticular route. In general, the ectoparasites of the hamster do not play an important role in the transmission of this parasite from host to host.

Hamsters are also susceptible to the other Leishmaniae, such as L. tropica, L. braziliensis, L. infantum, etc. Most of these parasites are susceptible usually only by the subcutaneous route.

The infections are visceral at first, followed by enlargement of the spleen and liver due to hyperplasia of the reticuloendothelial system. Peripheral lesions are then produced. The presence of these parasites induces a proteinuria which results in oedema. However, the general health of the hamsters is very slightly affected by the disease. This phenomenon was found to be the result of the presence of a large number of cells, clasmatocytes, in the peripheral blood which acted as a protective agent, they being large wandering phagocytes.

The tartar emetic group and antimony compounds have been almost entirely replaced by the diamidine compounds in the treatment of all types of leishmaniasis. The most efficient one is 4:4'-diamidino stilbene (stilbamidine). The therapeutic effect does not depend on the total amount of drug, but also

on the time distribution of the total amount.

There are three trypanosomes parasitic in hamsters, namely, Trypanosoma cricetuli, T. criceti, and T. rabinowitschi. Many authors believe that they are identical with the rat trypanosome, T. lewisi, although no success in transmitting T. lewisi to hamsters has ever been reported. Many extensive morphological studies have been done on these trypanosomes, however, and there seem to be distinct morphological differences in the structure of the nucleus, its position, and also the various dimensions of these three species.

Most of the work on trypanosome transmission has been done with T. criceti. It has been found that hamsters may be infected by the oral route by means of feces containing infective stages of the dog flea, Ctenocephalus canis. They may also be infected by means of blood containing trypanosomes. No conclusive evidence has been found on the ectoparasites as vectors. The pathology of this disease is usually inflammatory involving tissue damage.

The course of infection with trypanosomes in hamsters was found to be as follows: (1) an incubation period of 9 to 12 days; (2) period of division lasting 24 hours; and (3) a period of chronic infection lasting 5 months and over, during which allbthe trypanosomes are monomorphic. The condition found in (3) suggests that there is an inhibition of reproduction product in the blood of the hamsters, as in the case of the rats infected with T. lewisi. This product was shown to be pro-

duced by the spleen, since the trypanosomes continued to divide in splenectomized hamsters. The only preparation with any noticeable affect in the treatment of this disease is arsenophenylglyzin.

Numerous parasites of the hamster belong to the class Sporozoa. Three haemogregarines have been found, namely, Grahamella cricetuli Patton and Hindle 1926, Leucocytogregarina criceti Noller 1912, and one which was morphologically indistinguishable from G. alactagae. Three parasites belonging to the Coccidia have been found, one unidentified, and the other two were designated as types of Isospora freundi Yakimoff and Gousseff 1935. One sarcosporidian was found in the subcutaneous muscles of the back and pharynx of hamsters. It was considered as a new species and was named Sarcocystis cricetuli Patton and Hindle 1926. Nuttallia cricetuli Sprinholz- Schmidt 1937 was also found in the blood of hamsters.

Cestodes are the most common helminth parasites, three of them infecting hamsters. They are Hymenolepis straminea Goeze 1782, H. criceti Janicki 1904, and H. sinensis Oldham 1929. H. nana (Siebold 1852) Blanchard 1891, also parasitic in man, has been found to have a high incidence in hamsters. Therefore, care in the handling of these animals is stressed, since an infection with these tapeworms can become very serious by means of autoinfection.

The lesions produced by these tapeworms are only mechanical and not severe. There does not seem to be any defensive

reaction set up by the host.

There are only two cases of trematodes parasitic in hamsters. Hamsters have been experimentally infected with Schistosoma japonicum, one of the blood flukes, and naturally infected with Plagiorchis obensis, an intestinal fluke.

The nematodes which were found parasitic in hamsters either naturally or experimentally were: Litomosoides carinii, a filariid worm transmitted by the tropical rat mite, Liponyssus; Syphacia obvelata, an oxyurid also parasitic to man; and Heligmosoides travassos and H. yorkei, trichostrongylid parasites.

The ectoparasitic fauna of hamsters is made up mainly of lice, fleas, mites, a few ticks, and larval forms of ticks and Diptera. The lice found on hamsters are Haematopinus sps., Polyplax dentaticorium, and possibly Eremophthurius sps. The fleas of hamsters are Ctenocephalus canis, Ceratophyllus fasciatus, C. arvalis, C. tesquorum sp. sungarius, Ophthalmopsylla jettmari, Rhadinopsylla sps., Typhlopsylla assimilis, and Neopsylla bidentatiformis, the plague vector for hamsters.

Research on the experimental infection of hamsters showed that the hamster serves as an experimental host for the larval form of Toxascaris leonina, and for the larvae and very possibly the adults of Enterobius vermicularis, the human pinworm. No conclusive evidence was found that Hymenolepis diminuta develops in hamsters. Trichostrongylus sp., Trichocephalus trichiurus, Trichocephalus vulpis, Heterakis gal-

linae did not develop in hamsters. All hamsters were found to be free of parasites. No parasites were found to be present in the blood.

Since hamsters are swiftly becoming one of the most popular laboratory animals, more research on the susceptibility of hamsters to parasites infective also to man should be performed.

ABSTRACT

A review of the literature on the parasites of hamsters is presented.

The chapter on the leishmania deals with the susceptibility of hamsters to infection with all types of Leishmania and their epidemiology and histopathology. A brief resume of the treatment of leishmaniasis in hamsters is also presented.

The chapter on trypanosomes infective to hamsters is concerned mainly with morphological work and subsequent classification of these parasites. The epidemiology, histopathology, and treatment of trypanosomes is treated briefly.

Sporozoan parasites, representing all the orders of the Sporozoa except the Hemosporidia, are mentioned in a separate chapter.

Four species of tapeworms parasitize hamsters. The discovery of 4 nematodes and 2 trematodes of hamsters is described.

The chapter on the ectoparasites of hamsters lists the various arthropods found by examination of hamsters and also their nests. They consist mainly of fleas, lice, mites, ticks, and occasionally larval forms of arthropods.

An attempt was made to infect hamsters experimentally with various parasites. The parasites used were helminths. The methods used and the results are discussed. Toxascaris leonina and Enterobius vermicularis were successfully introduced in hamsters.

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